Cognitive dysfunctions in recreational and dependent cocaine users: role of attention-deficit hyperactivity disorder, craving and early age at onset

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Abstract: BACKGROUND: Dependent cocaine users consistently display cognitive deficits but cognitive performance of recreational cocaine users has rarely been investigated. AIMS: To examine whether cognitive performance is impaired in relatively pure recreational and dependent cocaine users. METHOD: The cognitive performance of recreational (n = 68) and dependent cocaine users (n = 30) was compared with the performance of stimulant-naive controls (n = 68) employing an extensive neuropsychological test battery. Moreover, the impact of attention-deficit hyperactivity disorder (ADHD) symptoms, craving and early age at onset was analysed. RESULTS: Dependent cocaine users display broad cognitive impairments in the domains of attention, working memory, declarative memory and executive functions. The performance of recreational cocaine users in all four domains was intermediate between that of controls and dependent users and they displayed significant deficits foremost in the domains of attention and working memory. In addition, ADHD symptoms, craving and age at onset were important modulators of cognitive function in cocaine users. CONCLUSIONS: Cognitive deficits occur at a recreational and non-dependent level of cocaine use. Cocaine use and ADHD seem to have mutually aggravating effects on cognitive impairment.

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Cognitive dysfunctions in recreational and dependent cocaine users: The role of ADHD, craving, and early age of onset

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Abstract

Background: Dependent cocaine users consistently display cognitive deficits but cognitive performance of recreational cocaine users has rarely been investigated so far.

Aims: To examine if cognitive performance is impaired in preferably pure recreational and dependent cocaine users.

Method: The cognitive performance of recreational (*n*=68) and dependent cocaine users (*n*=30) was compared with the performance of stimulant-naïve controls (*n*=68) employing an extensive neuropsychological test battery. Moreover, the impact of ADHD symptoms, craving, and early age of onset was analyzed.

Results: Dependent cocaine users display broad cognitive impairments in the domains of attention, working memory, declarative memory, and executive functions. Recreational cocaine users performed in all four domains intermediate between controls and dependent users and displayed significant deficits foremost in the domains attention and working memory. Importantly, ADHD symptoms, craving, and age of onset were important modulators of cognitive function in cocaine users.

Conclusions: Cognitive deficits already occur at a recreational and non-dependent level of cocaine use. Finally, cocaine use and ADHD seem to have mutually aggravating effects on cognitive impairment.

Declaration of interest: None.

Introduction

With an annual number of around 4 million users, cocaine is currently the second most frequent illicit drug in Europe.[1] Considering the addictive potential[2,3] and the negative health consequences,[2,4] the use of cocaine is still regarded as a major public health issue.[2,4]

For more than two decades, research has tried to examine the long-term impact of cocaine by focusing on dependent cocaine users (DCU). Evidence has accumulated that addictive cocaine use leads to neuroadaptive changes and dopaminergic alterations mainly exerted in the fronto-striatal network.[5-9] Imaging studies in chronic cocaine users have repeatedly reported reductions in gray matter density in the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate cortex, and the orbitofrontal cortex (OFC),[10-14] areas critically involved in several cognitive functions.[15] Accordingly, cognitive deficits in chronic cocaine users have been linked to structural and functional alterations primarily of the prefrontal cortex (PFC).[5,6,9,16]

The recent literature is characterized by the consensus that cocaine dependence is associated with significant neuropsychological impairment, while the aetiology and the severity of these impairments are matter of ongoing debate.[5,16-18] Existing studies with DCU indicate persisting cognitive impairments including deficits predominantly in the domains of attention, working and declarative memory, and, less consistently, in the heterogeneous concept of executive functions.[5,10,16-21] However, given that these previous studies differed in their inclusion and exclusion criteria regarding comorbid psychiatric diseases, polytoxic drug use history, abstinence time, and verification of self-reported drug intake, the specific impact of chronic cocaine use on cognitive processes was difficult to determine so far.

While most of these studies focused on the chronic misuse of cocaine, relatively little is known about the substantial number of recreational but non-dependent cocaine users (RCU).[1] Moreover, in comparison to studies with DCU, the investigation of RCU has several advantages, as they are I) not (or not yet) addicted, II) less burdened by psychiatric comorbidities,[22] III) rather unmedicated with psychotropic drugs, and IV) mostly display a reduced amount of polytoxic drug use. Only recently research has started to systematically investigate possible cognitive effects of recreational cocaine

use.[23] Preliminary data from small samples of RCU indicate that also small and infrequent doses of cocaine affect different cognitive components such as attention, memory, or components of executive functions.[23-29] However, these previous studies lack a unique definition of recreational cocaine use (recreational cocaine use was either defined by a limited amount of cocaine use or not matching dependency criteria according to DSM-IV criteria), mostly rely on simple self-reported of drug use without objective verification, or tested only very small and predominantly male samples with mainly polytoxic drug use patterns.

Accordingly, after more than two decades of research and despite the supposed public health effects, there is still no clarification on the relation between the extent of cocaine use and the characteristics of cognitive impairments. So far, analyses of regular cocaine users categorized in groups of differing consumption patterns are lacking. Consequently, we aimed to investigate a large sample of RCU, DCU, and matched stimulant-naïve healthy controls with a comprehensive neuropsychological test battery to examine if cognitive performance is impaired in preferably pure recreational and dependent cocaine users. Possible alterations would be a fundamental issue notably in regard to risk markers, prevention, and treatment implications.[5,12,20] We expect to find considerable cognitive deficits in DCU and similar but less pronounced cognitive impairments in RCU, as we recently reported deficits in early information processing and blue-yellow colour vision in RCU suggesting alterations of catecholamine neurotransmission already in RCU.[30,31] Although psychiatric comorbidities such as Attention-Deficit/Hyperactivity Disorder (ADHD) and depression are frequently present among DCU,[32,33] their separate impact on cognition was scarcely investigated so far. Thus, we conducted a comprehensive psychiatric diagnostic interview and additionally assessed symptoms of ADHD and depression with self-report questionnaires. Finally, by performing urine and hair toxicology analyses, we were uniquely able to objectively characterize not only recent drug use but also drug use over the past six months.

Methods and materials

Participants

Sixty-eight RCU, 30 DCU, and 68 cocaine-naïve control subjects were included in the study (recruitment and selection details **Methods DS1**). The three groups did not differ significantly for age, sex, smoking habits and verbal IQ. Exclusion criteria for all participants were acute or previous neurological disorders or head injury, any clinically significant medical diseases, and use of prescription drugs affecting the CNS. Additional exclusion criteria for the control subjects were all acute or previous Axis I DSM-IV psychiatric disorders including ADHD and any form of addiction except nicotine or regular illegal drug use (>15 occasions lifetime) with exception of occasional cannabis use. Specific exclusion criteria for the cocaine user groups were use of opioids, a polytoxic drug use pattern according DSM-IV, and acute or previous Axis I DSM-IV adult psychiatric disorders with exception of cocaine, cannabis, and alcohol abuse, history of affective disorders (acute major depression was excluded), or ADHD. None of the cocaine users was help-seeking in our department. Inclusion criteria for the two user groups were cocaine as primary drug, cocaine use of >0.5g per month, and an abstinence duration of <6 months. Cocaine dependence was diagnosed according to the Diagnostic and Statistical Manual-IV (DSM-IV) criteria[34], with only DCU fulfilling these criteria. Participants were asked to abstain from illegal substances for at least 72h and not to consume alcohol 24h before the testing session. Compliance with these instructions was controlled by urine and 6-month hair toxicologies (**Methods DS2**). The study was approved by the Cantonal Ethics Committee of Zurich. All participants provided written informed consent and were compensated for their participation.

Procedure

The present data were collected as part of the longitudinal Zurich Cocaine Cognition Study (ZuCo^{2}St).[31] Trained psychologists conducted a Structured Clinical Interview (SCID-I) according to DSM-IV procedures. Drug use was assessed by means of a structured and standardized Interview for Psychotropic Drug Consumption.[35] For the estimation of verbal intellectual performance, the Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B) was applied.[36] The brief version of the Cocaine

Craving Questionnaire (CCQ) was used to capture current cocaine craving.[37] Smoking habits were assessed by the Fagerström Test of Nicotine Dependence.[38] The Beck Depression Inventory (BDI)[39] measured the current severity of depression, and the ADHD self-rating scale (ADHD-SR)[40] focused on the diagnosis of ADHD in adulthood according to DSM-IV criteria. Subsequently, participants underwent a comprehensive neuropsychological test battery as described below. Participants were allowed to take a break at any time and smoking was permitted during the breaks.

Neuropsychological assessment

The test battery comprises four tests of the Cambridge Neuropsychological Test Automated Battery (CANTAB, wwwcantab.com): Rapid Visual Processing (RVP), Spatial Working Memory (SWM), Intra/Extradimensional Set Shifting (IED), Paired Associates Learning (PAL), a German version of the Rey Auditory Verbal Learning Test (RAVLT),[41] and the Letter Number Sequencing Task (LNST).[42] In regard to data reduction and specific analyses, 15 predefined main cognitive test parameters were z-transformed on the basis of means and standard deviations of the control group. These parameters were reduced to four in cocaine research commonly used[16-18,21] cognitive domains attention, working memory, declarative memory, and executive function according to theoretical a priori considerations (detailed description **Methods DS3**). Furthermore, these four z-scored domains were equally integrated into a global cognitive index (GCI).

Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics 19.0 (SPSS Inc.). Frequency data were analyzed by means of Pearson's Chi-square test and quantitative data by analyses of variance (ANOVA). Based on significant main effects, Sidak post-hoc comparisons were performed. To control for demographic inequalities, the variables age and verbal IQ were introduced as covariates in analyses of covariance (ANCOVA) with linear group contrasts. Correlation analyses (Pearson's product-moment) to relate drug use parameters to cognitive performance were conducted across a combined user group. Cumulated cocaine use and weekly use in grams were ln-transformed for statistical analyses because of the highly skewed distribution and the resulting deviation from the normal

distribution (Shapiro-Wilk W<.001). The effect of depression, ADHD, cocaine craving, recent cocaine use (positive urine test), and age of onset on cognitive performance was examined by correlation analyses and ANCOVA subgroup comparisons additionally corrected for severity of cocaine use. The effect of craving status was investigated because previous studies reported that food and nicotine has an impact on cognitive functioning.[43,44] Multiple logistic regressions were used to estimate odds ratios associated with the use of cocaine and cognitive performance. The odds ratios were left unadjusted because the values decisive for the group assignment were already adjusted for age and verbal IQ.

Results

Demographic characteristics and drug use

The groups did not differ regarding age, sex distribution, smoking status, and verbal IQ but DCU had fewer years of education than controls and RCU (**Table 1**). As expected, DCU displayed higher BDI and ADHD-SR sum scores than controls and RCU, while RCU showed higher scores than controls. As strived for, hair samples revealed a clear domination of cocaine compared to other illegal drugs (**Table 2**), whereby DCU showed a more than 8-fold higher concentration of cocaine and metabolites compared to RCU. Nonetheless, RCU were regular users with a mean weekly consumption of about 1g of cocaine but without fulfilling the DSM-IV criteria for dependence (41 RCU met the criteria for cocaine abuse). The main route of administration was intranasal, only three DCU were primarily inhaling the drug (2 free-base, 1 coca paste). In the urine samples, 10 RCU and 12 DCU tested positive for cocaine. However, we decided not to exclude them but to investigate the acute and post-acute effects of the drug.

****TABLE 1 & 2****

ANCOVA for the GCI showed a significant group effect including a clear linear trend ($p<.001$), and significant pairwise comparisons between all three groups (**Table 3; Figure 1; Figure DS1**), indicating global cognitive impairment in both cocaine user groups. Likewise, all four domains ($p<.001$) and 12 of 15 test parameters ($p<.05$-$.00001$, except the two IED parameters and the SWM strategy score) displayed significant linear trends, suggesting robust dose-response relationships. In all domains, RCU and DCU differed significantly from controls. Additionally, the domains working memory and executive functions showed significant group differences between RCU and DCU. The single test parameters within the attention, working memory, and declarative memory domains (detailed RAVLT analysis **Figure DS2)** showed similar results. However, the effect in the executive function domain was mainly driven by a strong effect regarding RAVLT recall consistency and, to a lesser degree, by the SWM strategy score, whereas the two IED parameters did not show any substantial group differences (detailed IED analysis **Figure DS3**).

****TABLE 3 & FIGURE 1****

Correlation analyses within the total group of cocaine users (n=98) revealed that the GCI and the domains working memory, declarative memory and executive functions were all inversely associated with cumulative cocaine dose, duration of cocaine use, cocaine metabolites benzoylecgonine and norcocaine in the hair, and a composite index reflecting the severity of cocaine use (**Table 4**; intercorrelation of cocaine use parameters **Table DS1**). Interestingly, the domain attention was only strongly correlated with the cumulative cocaine dose. The relatively high correlations in the domain executive functions were again driven by both the RAVLT and SWM parameter, while no associations were found for the two IED measures (single test correlation analysis **Table DS2**).

****TABLE 4****

ADHD, age of onset, craving, depression, and acute drug effects

Analysis of ADHD and craving subgroups by further splitting user groups according to predefined criteria[40] (yes/no fulfilling DSM-IV criteria in ADHD-SR) or median split (low/high, CCQ ≤16) suggested an impact of these variables on cognitive performance (**Figure 2**). ANCOVAs showed significant group effects for ADHD (F(4,158)=9.56, p<.001) and craving subgroups (F(4,158)=9.35, p<.001). While presence of craving additionally decreased cognitive performance only in RCU (d=.26)(**Figure 2b**), an ADHD diagnosis had a detrimental effect on cognitive functioning in both, RCU (d=.30) and DCU (d=.33)(**Figure 2a**). Notably, RCU and DCU without ADHD still significantly differed from controls. A combined analysis of ADHD and craving status in an integrated group of cocaine users confirmed this assumption by revealing a significant main effect for group (F(4,158)=7.66, p<.001), whereby the controls differed significantly from all cocaine user groups (**Figure 2c**). Age of onset of cocaine use played a crucial role (F(2,160)=10.92, p<.001), as users starting cocaine use before the age of 19 years performed significantly worse than users with a later age of onset (d=.66), whereby both users groups differed substantially from the control group ($d_{\leq 18}$=1.10, $d_{>18}$=.43)(**Figure 3**).

****FIGURE 2 & 3****

Splitting the user groups and controls according to a predefined depression criterion[45] (low/mild≤, BDI ≥11) showed a significant group effect ($F(5,157)=7.41$, $p<.001$) reflecting a weak additive impact of depressive symptoms on cognitive performance only in RCU ($d=.28$). Again, also non-depressed cocaine users differed significantly from non-depressed controls (**Figure DS4)**.

To test the influence of recent cocaine use, cocaine users were divided into users with positive ($n=22$, range: 217-24'888ng/ml, mean: 3'873ng/ml, SD: 6'461ng/ml) and users with negative urine samples ($n=75$) and compared with controls ($n=68$). Results revealed significant group effects for the GCI ($F(2,160)=14.76$, $p<.001$). Pairwise Sidak-comparisons yielded still significant and relatively strong differences between controls and both user groups ($d_{neg}=.63$, $d_{pos}=.84$), whereas users with positive urine sample showed slightly but non-significantly lower GCI scores than users with negative urine samples ($d=.22$). Similar patterns were found for all four domains (**Figure DS5**).

Multiple regression analyses conducted only in cocaine users confirmed that cumulative dose and duration of cocaine use were the best predictors of cognitive performance in contrast to psychopathological symptoms (**Table DS3**).

Risk threshold for cognitive impairments

As the use of cocaine proved to be an important determinant for cognitive performance, odds ratios were calculated to assess the risk for impairment when using cocaine. If a progressive clinical criterion of -1 SD was applied to define a cognitive decline, the use of cocaine indicated significant relative risks for deficits in attention (*OR*=3.52, *95% CI*=1.60-7.72, $p<.01$), working memory (*OR*=3.08, *95% CI*=1.47-6.49, $p<.01$), declarative memory (*OR*=2.40, *95% CI*=1.11-5.19, $p<.05$), and executive functions (*OR*=3.28, *95% CI*=1.53-7.04, $p<.01$). In summary, cocaine users were 3.8 times more likely to manifest global cognitive deficits (GCI) than controls (*OR*=3.80, *95% CI*=1.81-7.97, $p<.001$). If a conservative clinical criterion of -2 SD was applied, 1.5% ($n=1$) of the controls, 11.8% ($n=8$) of the RCU, and 30% ($n=9$) of the DCU revealed strong global cognitive impairment.

Additionally, **Figures 4a,b** illustrated a clearly increasing risk of cognitive impairment by growing cumulative doses of cocaine. While this classification emphasized the long-term impact of cocaine use for all four cognitive domains, declarative memory is the latest, whereas working memory is generally the earliest and most affected domain. Interestingly, a consumption of more than 1kg cocaine lifetime seemed to strongly enhance the risk for cognitive impairment (**Figure 4a**), while a consumption of more than 100g lifetime was associated with a ~50% risk for mild cognitive impairment (**Figure 4b**).

****FIGURE 4****

Discussion

The aim of the present study was to examine whether cognitive performance is impaired in recreational and dependent cocaine users. In contrast to previous studies, hair toxicologies and comprehensive psychiatric diagnostics allowed the investigation of preferably pure cocaine users with little psychiatric comorbidity. Moreover, this is the largest published sample of neuropsychologically examined cocaine users so far (*n*=98) and the first study directly comparing the cognitive performance of stimulant-naïve controls with both, RCU and DCU. The major finding of the present study is that rather intensive RCU showed small but significant cognitive dysfunction further deteriorating in DCU. RCU displayed the strongest effects in the attention domain, while in DCU working memory was most affected. Correlation and regression analyses revealed negative associations between cognitive performance and cocaine metabolites in the hair, cumulative cocaine dose, and duration of cocaine use suggesting that cognitive impairments might be partially cocaine-induced. Additionally, the influence of ADHD and cocaine craving on cognitive functioning of cocaine users was not systematically investigated before, a shortcoming that we overcame here. We found that symptoms of ADHD and depression as well as craving for cocaine are important modulators of cognitive function in cocaine users, whereas recent cocaine use seemed to be less important. However, cognitive dysfunction is still present in cocaine users without presence of craving, depression, or ADHD symptoms. Finally, we could demonstrate that the risk for cognitive impairment increases with early age of onset and ascending cumulative cocaine doses in particular if estimated lifetime doses of 500g to 1kg cocaine are exceeded (**Figure 4**).

The present results indicate impaired attention in both, RCU and DCU, with moderate to strong effect sizes, respectively. As attention involves several subprocesses, it should be emphasized that our domain is primarily based on two RVP parameters measuring sustained attention. Therefore, we replicated previous reports on sustained attention deficits in DCU[17,21] but extends the current knowledge regarding relatively pure RCU, as attentional deficits have previously been indicated only in small samples (*n*=13-18) of polytoxic RCU.[23,24,29]

Concerning working memory, the strong effect sizes found for DCU confirm previous findings also mostly drawn from much smaller samples.[17,18] Also in accordance with a recent study investigating a small sample of polydrug RCU (*n*=17), we found that relatively pure recreational cocaine use is associated with subtle visuo-spatial working memory impairment.[29] Additionally, our results firstly indicate small to moderate verbal working memory deficits in RCU.

Furthermore, we confirmed consistently revealed broad deficits of verbal[16,20,21] and visual learning and memory[16,17,20] in DCU. The only report analyzing RCU described similar verbal memory deficits for recreational prescription stimulant users with >80% cocaine co-use, but found no significant effects in a small group (*n*=13) of pure RCU with a low minimal inclusion threshold (three uses in past 6 months).[28] Thus, declarative memory dysfunction is associated not only with chronic, but also with recreational cocaine use. However, compared to other domains declarative memory seemed to be least affected at cumulative cocaine doses <500g.

Unlike in the other domains, the single executive function parameters displayed inconsistent results. Both IED parameters indicated no performance deficits in the user groups. On the contrary, the SWM strategy score demonstrated small to moderate, and the RAVLT recall consistency moderate to strong effects in RCU and DCU. These inconsistencies are typical for the heterogeneous concept of executive functions reflecting varying task requirements and difficulty levels between studies.[17] Nevertheless, the existing literature reported executive deficits in DCU rather on complex than on simple tasks.[17] As 71% of the subjects in the user groups achieved the highest IED stage, a ceiling effect can be assumed. Furthermore, we found strong correlations between the executive domain and several cocaine use parameters confirming similar relationships that were found in earlier studies on DCU[19] and RCU.[26]

Sustained attention and working memory processes are both associated with increased activity in prefrontal, parietal, and cingulate brain regions.[15] Accordingly, the LNST involves the lateral PFC,[46] the SWM performance is associated with the DLPFC and VLPFC,[47,48] and the PAL depends on frontal and medial temporal lobe function.[49] In depths analysis of the RAVLT revealed that cocaine users primarily display learning and retrieval deficits, while recognition was less affected – a pattern specifically reported for PFC lesions.[50] Likewise, PCF lesions have been related to impairments in

recall consistency.[51,52] Finally, glucose metabolism in the DLPFC significantly predicted visual and verbal memory performance in cocaine addicted subjects and controls.[16] Together with previous findings that DCU display decreased gray matter volume and glucose metabolism in the OFC and DLPFC[10-14,53-56] the neuropsychological profile therefore suggests that similar but less pronounced alterations of the PFC might be present in RCU.

We investigated potential co-factors frequently associated with cocaine use or commonly addressed as confounding factors for cognition such as ADHD and depressive symptoms.[32,57] Moreover, craving for food[43] and nicotine[44] has been shown to have an impact on cognitive functioning but the specific impact of cocaine craving has not been investigated so far. Here, high craving and depression scores or an ADHD diagnosis further decreased the cognitive performance within the group of RCU. Additionally, DCU with clinically relevant ADHD symptoms displayed stronger cognitive deficits (d=1.37) than DCU without ADHD (d=1.04), while neither craving nor depression symptoms had an additional effect in this group. Importantly, cocaine users without clinically relevant ADHD or depression scores and also with low craving scores still displayed significant cognitive deficits, whereas a combination of an ADHD diagnosis and high craving lead to the strongest impairments, similar to our results on early information processing.[31] Regarding the impact of depression, our findings confirm a previous result reporting no additional effect of dysphoria on cognitive performance in a sample of predominantly DCU[18] but our data additionally indicate a small impact of depression at a recreational level of use.

ADHD is characterized by problems in attentional performance and inhibitory control and patients with ADHD on average perform worse than healthy controls on tests of attention and executive function.[58] Nevertheless, the influence of ADHD symptoms on the cognition of cocaine users, in which ADHD is highly prevalent, was not investigated so far. The exact pathogenesis underlying ADHD is still unknown,[59] but as abnormalities within catecholamine systems and the PFC seem to play a major role in ADHD[59,60] and cocaine use,[7,8] it can be assumed that similar pathologies might lead to a mutual aggravation of detrimental effects on cognitive performance.

In contrast to a previous finding, showing that cocaine users with a positive urine toxicology have slightly improved cognitive performances,[18] users with positive cocaine urine tests displayed only

slightly worse cognitive scores in the present study. As urine toxicologies were performed by immunoassays, which are only presumptive and potentially biased by external factors,[61] positive urine tests were not by all means a violation of the requested three day cocaine retention period.

Study Limitations and Future Research

The study has some limitations: I) Cocaine dependency was diagnosed according to the DSM-IV criteria.[34] These criteria depend on self-perception but do not consider features such as duration and amount of cumulative doses. Thus, some subjects in the RCU group might be misclassified as non-dependent. II) Although this is one of the first investigations employing hair analysis in a neurocognitive study with cocaine users, we can only rely on self-reports for all illegal drug use prior to 3 to 6 months (depending on hair length). This is, however, an inevitable constraint of all studies with illegal drug users.[62] III) A cross-sectional design cannot determine whether these cognitive deficits in cocaine users are pre-existent traits (vulnerability or resilience), drug-induced consequences, or both. Hence, to answer this question we need to await the findings of the second part of the ZuCo^{2}St longitudinal study in 2013. IV) As cocaine users participating voluntary in a study session lasting several hours feature a certain level of motivation and cognitive functionality, we assume that the cocaine users in our sample are not the most impaired subjects and probably even perform relatively well. Thus, the cognitive impairments shown here might partially be underestimated for both, RCU and DCU.

Conclusion

The results confirmed that dependent cocaine use is associated with broad cognitive impairments in the domains attention, working memory, declarative memory, and parts of the executive functions. In all four domains, recreational users performed intermediate between controls and dependent users and displayed significant deficits predominantly in the domains attention and working memory, which is in line with our previous work indicating catecholamine dysfunction already at a recreational level of use.[30,31] Furthermore, all cognitive domains displayed correlations with the long-term intake parameters duration and amount of cocaine use and specifically early age of onset was linked to

considerable cognitive dysfunction. The neuropsychological profile suggests PFC dysfunction as the common denominator of these cognitive impairments, which is in line with previous findings showing alterations of the frontostriatal dopamine system in addicted cocaine users.[9,53,54] Additionally, cocaine use and ADHD seem to have mutually aggravating effects on cognitive impairments. Altogether these results indicate gradual impairments in both, recreational and dependent cocaine users, while clinically relevant cognitive deficits seem to arise with long-term cocaine use as best reflected by cumulative cocaine dose.

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Table 1 Demographic data

	Stimulant-naïve controls	Recreational cocaine users	Dependent cocaine users	Value[a]	df, df_{err}	p
N	68 (41%)	68 (41%)	30 (18%)			
Age, y	30.3 (9.2)	28.7 (6.2)	32.5 (9.0)	F=2.386[a]	2, 163	.10
Sex (f/m)	21 / 47	18 / 50	8 / 22	x^2=0.375[b]	2	.83
Smoking (y/n)	53 / 15	53 / 15	24 / 6	x^2=0.061[b]	2	.97
Verbal IQ (MWT-B)	104.4 (9.7)	103.2 (9.6)	99.7 (9.1)	F=2.457[a]	2, 163	.09
School education, y	10.7 (1.8)	10.5 (2.0)	9.5 (1.2)**°	F=4.822 [a]	2, 163	**.01**
BDI sum score (0-63)	4.6 (4.4)	7.4 (6.1)*	11.8 (8.6)***°°	F=15.009 [a]	2, 163	**<.001**
BDI depression status (y/n)[d]	5 / 63	17 / 51	12 / 18	x^2=15.066[b]	2	**<.001**
ADHD-SR sum score (0-22)	7.6 (4.8)	13.2 (9.0)***	17.1 (8.7)***°	F=19.517 [a]	2, 163	**<.001**
ADHD DSM IV (y/n)[e]	0 / 68	14 / 54	8 / 22	x^2=18.266[b]	2	**<.001**
Craving for cocaine (0-70)	-	19.0 (9.1)	20.3 (11.4)	T=0.598[c]	1, 96	.55

Means and standard deviations. Significant p values are shown in bold. Sex, smoking, BDI depression status, and ADHD-SR DSM-IV are shown in frequency data.
[a] ANOVA (all groups), [b] χ^2 test (all groups) for frequency data, or [c] independent t-test (cocaine users only)
[d] BDI, Beck Depression Inventory (cut-off ≥11)
[e] ADHD-SR, ADHD self rating scale (cut-off DSM-IV criteria)
[*] Significant Sidak post-hoc test vs. control group: *p<.05; **p<.01; ***p<.001
[°] Significant Sidak post-hoc test vs. RCU group: °p<.05; °°p<.01

Table 2 Pattern and amount of drug use

	Stimulant-naïve controls (n=68)	Recreational cocaine users (n=68)	Dependent cocaine users (n=30)
Alcohol			
Grams per week[a]	116.8 (122.6)	167.8 (117.5)	188.5 (260.6)
Years of use	13.2 (9.3)	11.2 (5.1)	13.5 (9.5)
Nicotine			
Cigarettes per day[a]	9.3 (9.5)	11.7 (8.8)	15.7 (13.5)
Years of use	9.2 (9.2)	9.6 (6.4)	14.2 (9.3)
Cocaine			
Times per week[a]	-	1.1 (1.0)	2.9 (2.6)
Grams per week[a]	-	1.1 (1.4)	7.9 (15.8)
Years of use	-	6.5 (4.0)	9.4 (6.5)
Maximum dose (grams/day)	-	3.5 (2.5)	9.4 (8.4)
Cumulative dose (grams)	-	519.7 (751.2)	5500.9 (9635.2)
Last consumption (days)[b]	-	27.5 (37.6)	21.0 (33.6)
Hair analysis Cocaine pg/mg[c]	-	2739 (4628)	22164 (32609)
Hair analysis Benzoylecgonine pg/mg[c]	-	546 (919)	5048 (7711)
Hair analysis Cocaethylene pg/mg[c]	-	276 (316.)	2006 (3656)
Hair analysis Norcocaine pg/mg[c]	-	62 (101)	586 (758)
Hair analysis $Cocaine_{total}$ pg/mg[c,e]	-	3347 (5580)	27798 (40226)
Urine toxicology (neg/pos)[d]	68 / 0	57 / 10	18 / 12
Cannabis			
Grams per week[a]	0.5 (1.0)	0.9 (2.1)	1.2 (3.7)
Years of use	4.7 (6.5)	7.7 (6.0)	10.5 (9.9)
Cumulative dose (grams)	358.3 (846.2)	1042.8 (1780.0)	3550.3 (5959.0)
Last consumption (days)[b]	36.2 (50.1); n=33	22.1 (32.3); n=44	25.7 (32.8); n=20
Urine toxicology (neg/pos)[d]	58 / 10	55 / 12	20 / 10

Table 2 Pattern and amount of drug use (cont)

	Stimulant-naïve controls (n=68)	Recreational cocaine users (n=68)	Dependent cocaine users (n=30)
Amphetamine			
Grams per week[a]	0.0 (0.0)	0.1 (0.2)	0.0 (0.2)
Years of use	0.0 (0.1)	1.6 (3.0)	1.5 (3.2)
Cumulative dose (grams)	0.2 (1.4)	21.2 (56.8)	22.3 (62.8)
Last consumption (days)[b]	121.6 (0.0), n=1	61.8 (51.3); n=25	78.4 (75.4); n=6
Hair analysis Amphetamine pg/mg[c]	1 (7)	76 (257)	60 (169)
MDMA			
Tablets per week[a]	-	0.1 (0.3)	0.4 (1.8)
Years of use	0.3 (1.7)	2.5 (3.8)	3.1 (5.2)
Cumulative dose (tablets)	0.9 (2.9)	35.9 (90.5)	157.4 (393.5)
Last consumption (days)[b]	-	75.1 (84.8); n=20	82.1 (45.4); n=9
Hair analysis MDMA pg/mg[c]	3 (16)	545 (1598)	255 (653)
GHB			
Cumulative dose (pipettes)	0.0 (0.0)	1.8 (9.5)	1.3 (2.9)
Hallucinogens			
Cumulative dose (times)	0.9 (2.2)	6.0 (14.6)	6.9 (11.8)

Means and standard deviations. Use frequency, duration of use, and cumulative doses are averaged within the total group.
[a] Average use during the last 6 months.
[b] Last consumption is averaged only for persons who used the drug in the last 6 months. In this case, sample size (n) is shown.
[c] Cut-off values for cocaine = 500 pg/mg and for amphetamines/MDMA = 200 pg/mg.[63] Hair samples were voluntary and are deficient for 3 controls and 1 RCU.
[d] Cut-off values for cocaine = 150 ng/ml and for Tetrahydrocannabinol 50 ng/ml.[64] Urine toxicology test was deficient for 1 RCU.
[e] $Cocaine_{total}$ (= Cocaine + Benzoylecgonine + Norcocaine) is a more robust procedure for discrimination between incorporation and contamination of hairs.[65]

Table 3 Neurocognitive global and domain z-scores and scores of neuropsychological tests

Measure	n[a]	Stimulant-naïve controls	Recreational cocaine users	Dependent cocaine users	F	df, df_{err}	p	p, Sidak post-hoc Controls vs. RCU	p, Sidak post-hoc Controls vs. DCU	p, Sidak post-hoc RCU vs. DCU	Cohen's d Controls vs. RCU	Cohen's d Controls vs. DCU	Cohen's d RCU vs DCU
Global Cognitive Index	68/68/30	-0.02 (0.06)	-0.35 (0.06)	-0.67 (0.09)	19.345	2, 161	**<.001**	**<.001**	**<.001**	**.01**	0.53	1.04	0.52
Neurocognitive domain scores													
Attention	68/68/30	-0.03 (0.10)	-0.41 (0.10)	-0.68 (0.15)	7.579	2, 161	**<.001**	**.02**	**.001**	.38	0.44	0.74	0.30
Working memory	68/68/30	-0.03 (0.08)	-0.36 (0.08)	-0.81 (0.12)	16.312	2, 161	**<.001**	**.007**	**<.001**	**.005**	0.43	1.00	0.58
Declarative memory	68/68/30	-0.02 (0.09)	-0.4 (0.09)	-0.67 (0.15)	8.333	2, 161	**<.001**	**.01**	**<.001**	.34	0.43	0.73	0.30
Executive functions	68/68/30	-0.02 (0.06)	-0.22 (0.06)	-0.5 (0.09)	11.388	2, 161	**<.001**	**.03**	**<.001**	**.02**	0.39	0.92	0.54
Neuropsychological test scores													
Attention													
RVP Discrimination performance A'	67/68/30	0.917 (0.0)	0.899 (0.0)	0.885 (0.0)	6.254	2, 160	**.002**	**.04**	**.004**	.43	0.42	0.72	0.31
RVP Total hits	67/68/30	18.3 (0.5)	16.5 (0.5)	15.3 (0.8)	5.561	2, 160	**.005**	**.05**	**.008**	.53	0.40	0.67	0.27
RAVLT Supraspan trial 1	68/68/30	8.9 (0.2)	8.4 (0.2)	8.0 (0.4)	2.407	2, 161	.09	.31	.13	.81	0.25	0.41	0.17
Working memory													
LNST Score	68/68/30	15.6 (0.3)	14.5 (0.3)	13.2 (0.5)	8.320	2, 161	**<.001**	.07	**<.001**	.07	0.34	0.78	0.44
SWM Total errors	68/67/30	20.1 (1.9)	23.3 (1.9)	34.5 (2.9)	8.727	2, 160	**<.001**	.53	**<.001**	**.005**	0.19	0.84	0.65
PAL First trial memory score	68/67/30	15.6 (0.4)	14.1 (0.4)	13.4 (0.6)	6.575	2, 160	**.002**	**.02**	**.005**	.67	0.43	0.64	0.21
Declarative memory													
RAVLT Learning performance (∑ trials 1-5)	68/68/30	62.0 (0.9)	58.0 (0.9)	54.9 (1.4)	9.612	2, 161	**<.001**	**.009**	**<.001**	.22	0.45	0.80	0.35
RAVLT Adjusted recognition performance p(A)	68/68/30	0.873 (0.0)	0.858 (0.0)	0.823 (0.0)	2.076	2, 161	.13	.83	.12	.39	0.13	0.44	0.31
RAVLT Delayed recall trial 7	68/68/30	13.1 (0.3)	11.9 (0.3)	11.4 (0.5)	6.046	2, 161	**.003**	**.02**	**.009**	.75	0.44	0.63	0.19
PAL Total errors adjusted	68/67/30	10.6 (1.4)	15.1 (1.4)	16.9 (2.2)	3.852	2, 160	**.02**	.08	.05	.88	0.35	0.49	0.14
PAL Total trials adjusted	68/67/30	8.5 (0.3)	9.5 (0.3)	10.1 (0.5)	4.231	2, 160	**.02**	.09	**.03**	.72	0.34	0.53	0.19
Executive functions													
IED Total errors adjusted	68/68/30	30.3 (4.1)	31.3 (4.1)	32.3 (6.3)	.039	2, 161	.96	1.00	.99	1.00	0.03	0.06	0.03
IED Total trials adjusted	68/68/30	104.1 (7.2)	107.3 (7.3)	108.5 (11.2)	.075	2, 161	.93	.98	.98	1.00	0.05	0.07	0.02
SWM Strategy score	68/67/30	32.7 (0.6)	33.4 (0.6)	34.9 (0.9)	1.887	2, 160	.15	.84	.15	.43	0.12	0.42	0.30
RAVLT Recall consistency in %	68/68/30	92.3 (1.1)	88.1 (1.1)	83.3 (1.6)	11.004	2, 161	**<.001**	**.02**	**<.001**	**.05**	0.43	0.92	0.49

Means and standard errors. ANCOVA (all groups, corrected for age and verbal IQ). Significant p values are shown in bold.
GCI and cognitive domain scores are z-transformed values.
The robustness of these parametric tests was confirmed using bootstrap simulations with 1000 replications. Thereby, only one pairwise Sidak post-hoc comparison above turned from a significant group difference into a statistical trend (RAVLT recall consistency; cocaine rec vs. cocaine dep $p_{post\text{-}hoc}$=.08).
[a] Sample size control group/RCU/DCU. In each of the tasks RVP, PAL, and SWM one subject is missing due to a technical failure.

Table 4 Correlations between neurocognitive global and domain z-scores and cocaine use parameters in cocaine users

	n	Global Cognitive Index	Attention	Working memory	Declarative memory	Executive functions
Cumulative dose (grams) log[a]	98	***-.50	**-.31	***-.39	***-.43	***-.42
Cumulative dose (grams) log, adj. for age[b]	98	***-.47	***-.34	***-.34	***-.39	***-.37
Times per week[a]	98	-.17				*-.25
Grams per week log[a]	98					
Years of use[a]	98	***-.33		***-.33	**-.29	***-.40
Years of use, adj. for age[b]	98	**-.28		*-.25	*-.22	***-.35
Maximum dose (grams/day)[a]	98	**-.26	*-.23		**-.27	
CCQ sum score (0-70)[a]	98			-.18		
Hair analysis Cocaine pg/mg[a]	97[c]	*-.22			-.20	-.18
Hair analysis Benzoylecgonine pg/mg[a]	97[c]	**-.29	-.17	*-.24	**-.28	*-.20
Hair analysis Cocaethylene pg/mg[a]	97[c]					
Hair analysis Norcocaine pg/mg[a]	97[c]	**-.28		**-.26	**-.27	*-.21
Hair analysis $Cocaine_{total}$ pg/mg[a]	97[c]	*-.24		-.17	*-.22	-.19
Severity of cocaine use Index[d]	98	***-.40	*-.21	**-.28	***-.37	***-.42

Correlations with a p-level below 10% are shown, while significant correlations are marked: *p<.05; **p<.01; ***p<.001
[a] Pearson's product-moment correlation
[b] Partial Correlation corrected for age
[c] Hair samples were voluntary and are deficient for 1 RCU
[d] Severity of cocaine Index use corresponds to the mean of the z-transformed parameters cumulative dose, grams per week, years of use, maximum dose, and hair analysis $Cocaine_{total}$

Figure legends

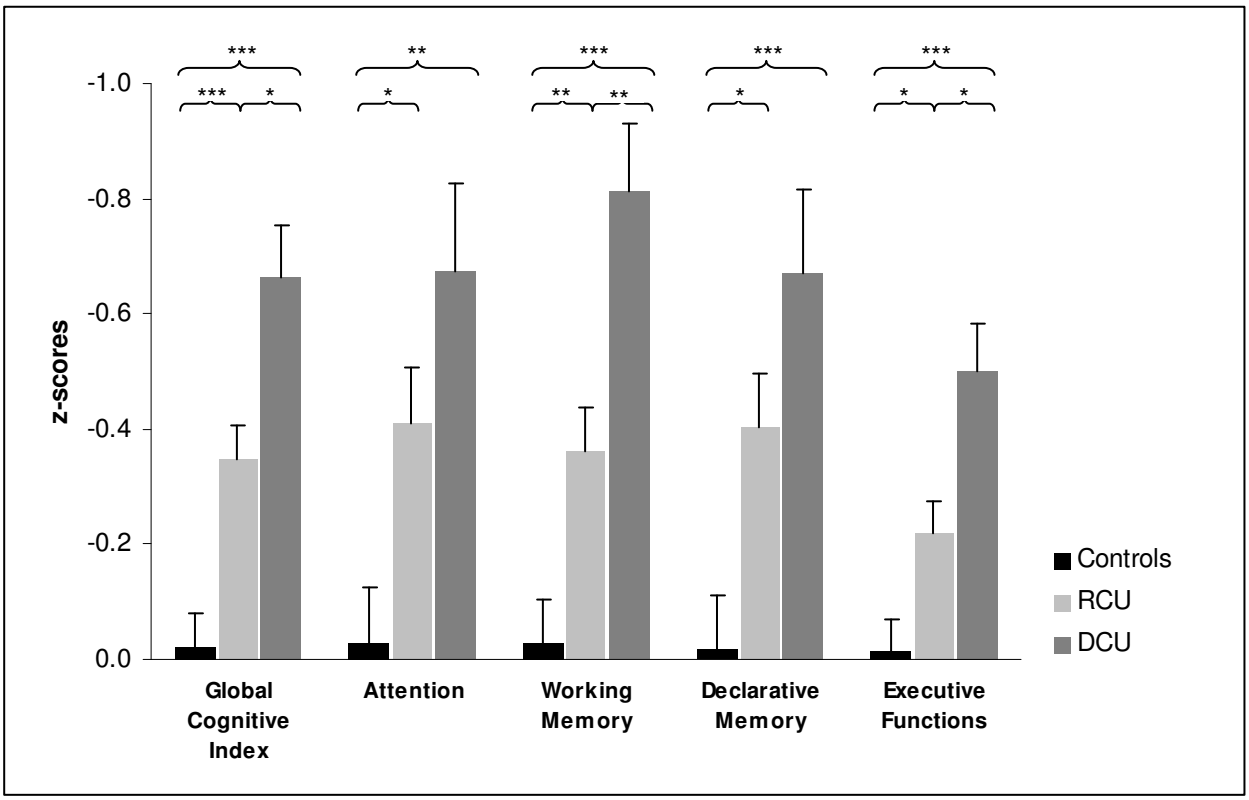
Figure 1: Mean z-scores and standard errors for the global cognitive index (GCI) and the four cognitive domains (values corrected for age and verbal IQ). Sidak post-hoc tests: *p<.05; **p<.01; ***p<.001.

Figure 2: Mean global cognitive index (GCI) scores and standard errors in groups stratified for cocaine use and confounding variables (values corrected for age, verbal IQ, and cocaine gram/week). Significant Sidak post-hoc test vs. control group: *p<.05; **p<.01; ***p<.001. Cohen's d vs. control group. **(a)** ADHD, DSM-IV criteria based on ADHD-SR. **(b)** CCQ, craving for cocaine status based on median split ≤16. **(c)** Combined user group (n=98) stratified for ADHD, DSM-IV criteria based on ADHD-SR and CCQ, craving for cocaine status based on median split ≤16.

Figure 3: Mean GCI scores and standard errors in groups stratified for age of onset for cocaine use (values are corrected for age, verbal IQ, and cocaine use in years). Group sizes (n) are shown. Significant Sidak post-hoc test vs. reference control group: **p<.01; ***p<.001. Cohen's d vs. control group.

Figure 4: (a) Percentage of cocaine users fulfilling the clinical cognitive criterion of below -1 SD in the specific cumulative dose group. **(b)** Percentage of cocaine users fulfilling the clinical cognitive criterion of below -1 SD in groups with from left to right ascending cumulative doses. Domain cut-offs: GCI SD=-.54, Attention SD=-.81, Working memory SD=-.70, Declarative memory SD=-.82, Executive functions SD=-.38. Values are corrected for age and verbal IQ.

Figure 1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-1.0
-0.8
-0.6
-0.4
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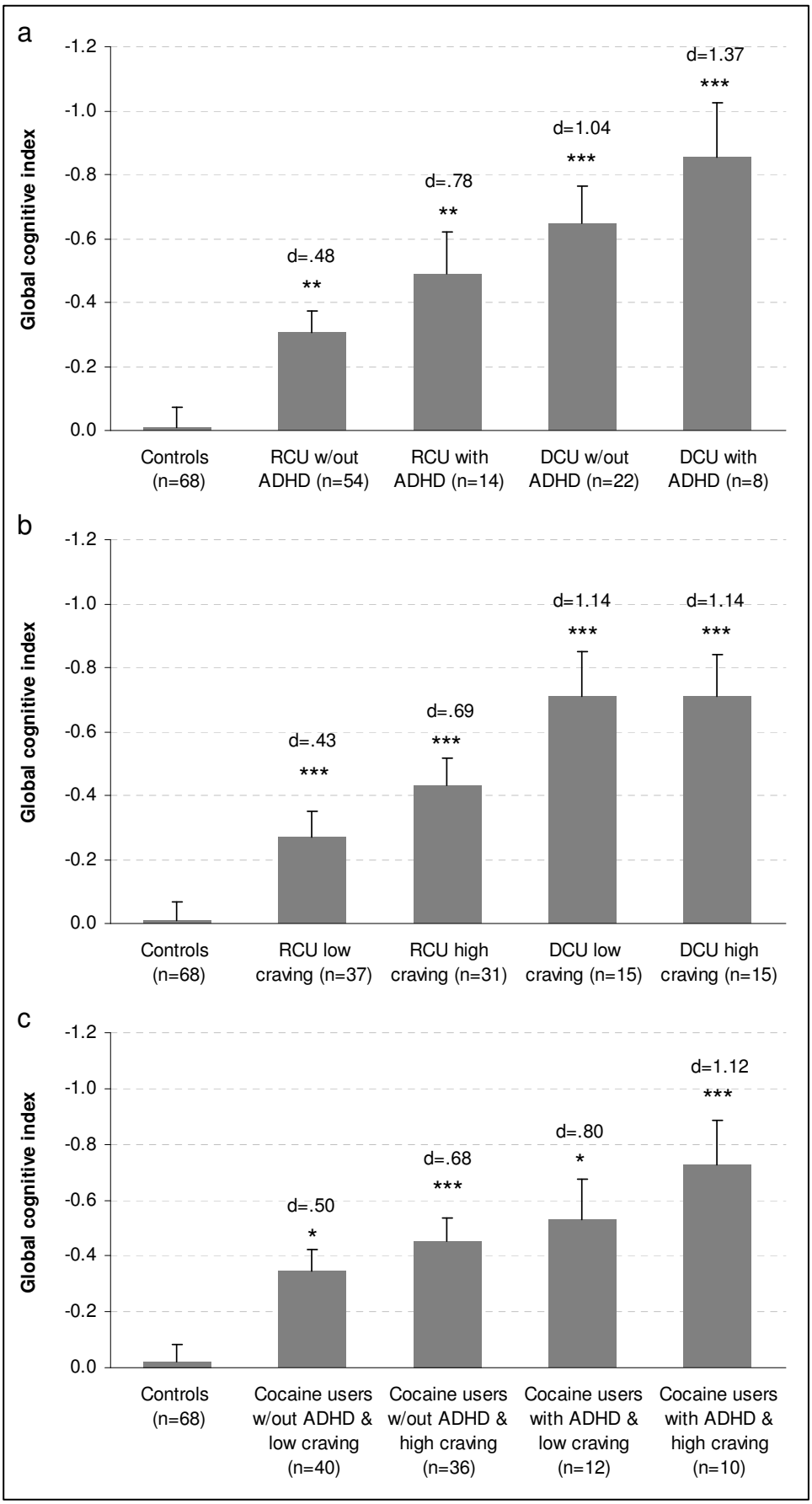
z-scores
Global Cognitive Index
Attention
Working Memory
Declarative Memory
Executive Functions
Controls
RCU
DCU

Figure 2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Global cognitive index
-1.2
-1.0
-0.8
-0.6
-0.4
-0.2
0.0
d=.48
**
d=.78
**
d=1.04
***
d=1.37
***
Controls (n=68)
RCU w/out ADHD (n=54)
RCU with ADHD (n=14)
DCU w/out ADHD (n=22)
DCU with ADHD (n=8)
b
Global cognitive index
d=.43
***
d=.69
***
d=1.14
***
d=1.14
***
Controls (n=68)
RCU low craving (n=37)
RCU high craving (n=31)
DCU low craving (n=15)
DCU high craving (n=15)
c
Global cognitive index
d=.50
*
d=.68
***
d=.80
*
d=1.12
***
Controls (n=68)
Cocaine users w/out ADHD & low craving (n=40)
Cocaine users w/out ADHD & high craving (n=36)
Cocaine users with ADHD & low craving (n=12)
Cocaine users with ADHD & high craving (n=10)

Figure 3

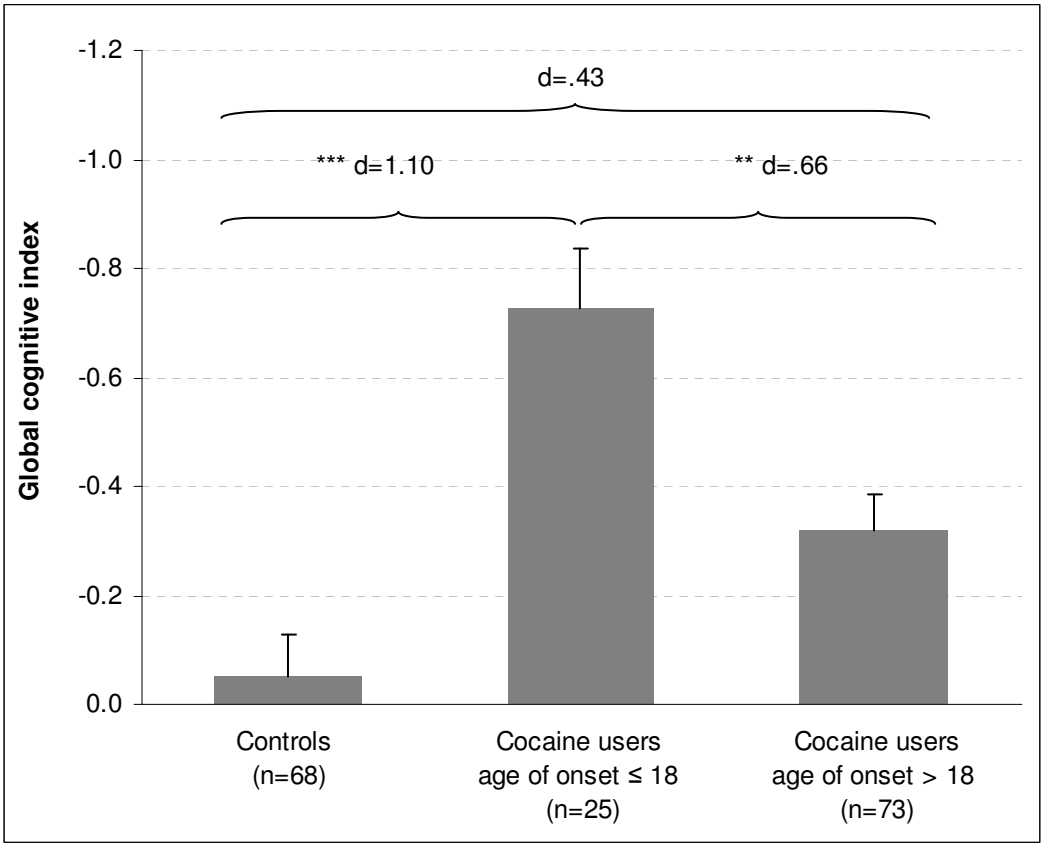
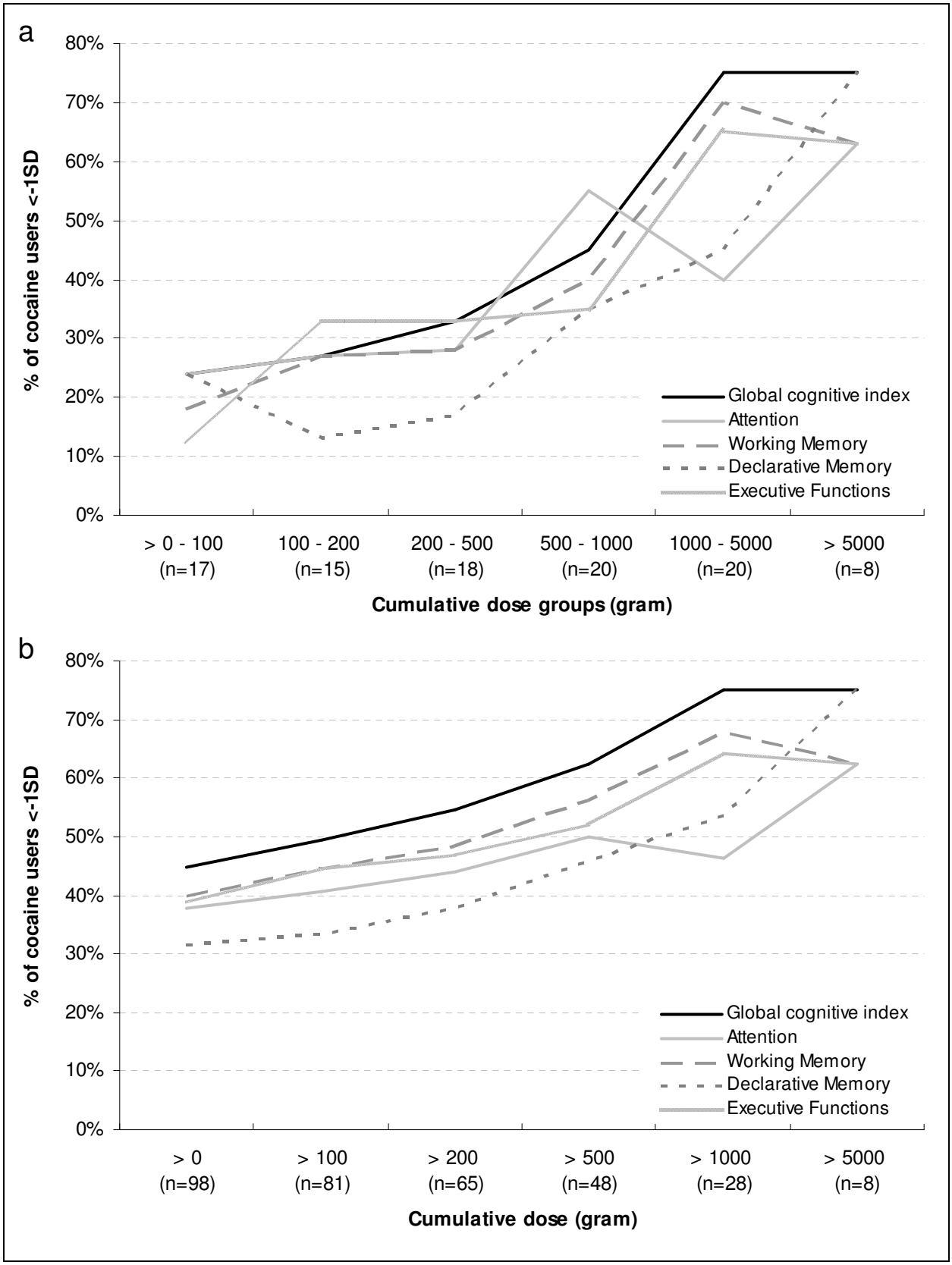

-1.2
-1.0
-0.8
-0.6
-0.4
-0.2
0.0
Global cognitive index
d=.43
*** d=1.10
** d=.66
Controls
(n=68)
Cocaine users
age of onset ≤ 18
(n=25)
Cocaine users
age of onset > 18
(n=73)

Figure 4


a
80%
70%
60%
50%
40%
30%
20%
10%
0%
% of cocaine users <-1SD
Global cognitive index
Attention
Working Memory
Declarative Memory
Executive Functions
> 0 - 100 (n=17)
100 - 200 (n=15)
200 - 500 (n=18)
500 - 1000 (n=20)
1000 - 5000 (n=20)
> 5000 (n=8)
Cumulative dose groups (gram)
b
80%
70%
60%
50%
40%
30%
20%
10%
0%
% of cocaine users <-1SD
Global cognitive index
Attention
Working Memory
Declarative Memory
Executive Functions
> 0 (n=98)
> 100 (n=81)
> 200 (n=65)
> 500 (n=48)
> 1000 (n=28)
> 5000 (n=8)
Cumulative dose (gram)

Data Supplement

Cognitive dysfunctions in recreational and dependent cocaine users: The role of ADHD, craving, and early age of onset

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Methods DS1: Recruitment and selection

The recruitment focused on the greater area of Zurich and lasted from January 2010 until January 2012. Participants were recruited via advertisements in local newspapers, online media, drug prevention and treatment centers, psychiatric hospitals, and by word of mouth. Eight-hundred-four prospective participants underwent a standardized telephone interview, whereof 240 subjects were considered to be eligible for the study at the University Hospital of Psychiatry in Zurich. All subjects were aged between 18 and 60 years and had sufficient German language skills. Forty-six participants had to be excluded afterwards due to hair analyses revealing illegal drug use not declared in the interviews (e.g., opioids, excessive MDMA use), or lack of cocaine use. Furthermore, the data of four participants (3 controls, 1 cocaine user) could not be analyzed because of technical problems during the test session and 24 participants were excluded due to matching reasons (age, verbal IQ, and smoking) between groups (15 controls, 9 cocaine users). Hair samples were provided by 163 subjects, as hair analysis was not possible due to an insufficient amount of hair for two controls and one cocaine user.

Methods DS2: Urine and hair toxicologies

Urine toxicology analyses comprised the compounds/substances: tetrahydrocannabinol, cocaine, amphetamines, benzodiazepines, opioids, and methadone and were assessed by a semi-quantitative enzyme multiplied immunoassay method using a Dimension RXL Max (Siemens, Erlangen, Germany).
To characterize drug use over the last six months objectively, hair samples were collected and analyzed with Liquid chromatography-tandem mass spectrometry (LC-MS/MS). If participants' hair was long enough, one sample of six cm hair (from the scalp) was taken and subsequently divided into two subsamples of three cm length. The following compounds were assessed: cocaine, benzoylecgonine, ethylcocaine, norcocaine, amphetamine, methamphetamine, MDMA, MDEA, MDA, morphine, codeine, methadone EDDP (primary methadone metabolite), tramadol, and methylphenidate.
For our routine protocol for drugs of abuse analysis a three step washing procedure with water (2 minutes shaking, 15ml), acetone (2min., 10ml) and finally hexane (2min., 10ml) of hair was performed. Then the hair samples were dried at ambient temperatures, cut into small snippets and extracted in two steps, first with methanol (5ml, 16hours, ultrasonication) and a second step with 3 ml MeOH acidified with 50 µL hydrochloric acid 33 % (3 hours, ultrasonication). The extracts were dried and the residue reconstituted with 50 µL MeOH and 500 µL 0.2 mM ammonium formate (analytical grade) in water. As internal standards deuterated standards of the following compounds were used, added as mixture of the following compounds: cocaine-d3, benzoylecgonine-d3, ethylcocaine-d3, morphine-d3, MAM-d3, codeine-d3, dihydrocodeine-d3, amphetamine-d6, methamphetamine-d9, MDMA-d5. MDEA-d6, MDA-d5, methadone-d9, EDDP-d3, methylphenidate-d9, tramadol-d3, oxycodone-d3, and ephedrine-d3. All deuterated standards were from ReseaChem (Burgdorf, Switzerland), the solvents for washing and extraction were of analysis grade and obtained from Merck (Darmstadt, Germany); LC-solvents were of HPLC grade and were obtained from Sigma Aldrich (Buchs, Switzerland).
The LC-MS/MS apparatus was an ABSciex QTrap 3200 (Analyst software Version 1.5, Turbo V ion source operated in the ESI mode, gas 1, nitrogen (50 psi); gas 2, nitrogen (60 psi); ion spray voltage, 3500V; ion source temperature, 450°C; curtain gas, nitrogen (20 psi) collision gas, medium), with a Shimadzu Prominence LC-system (Shimadzu CBM 20 A controller, two Shimadzu LC 20 AD pumps including a degasser, a Shimadzu SIL 20 AC autosampler and a Shimadzu CTO 20 AC column oven, Shimadzu, Duisburg, Germany). Gradient elution was performed on a separation column (Synergi 4µ POLAR-RP 80A, 150x2.0 with a POLAR-RP 4x2.0 Security Guard Cartridge, (Phenomenex, Aschaffenburg, Germany). The mobile phase consisted of 1mM ammonium formate buffer adjusted to pH 3,5 with formic acid (eluent A) and acetonitrile containing 1mM ammonium formate and 1 mM formic acid (eluent B). The Analysis was performed in MRM mode with two transitions per analyte and one transition for each deuterated internal standard, respectively.

Methods DS3: Construction of cognitive domain scores

Fifteen predefined main cognitive test parameters were z-transformed on the basis of means and standard deviations of the control group. Two cocaine users were missing either SWM or PAL parameters due to technical problems. These values were excluded from the domain computation. If necessary, test scores were reversed so that high scores always indicated a better cognitive performance. These parameters were reduced to the four the cognitive domains attention, working memory, declarative memory, and executive function according to theoretical a priori considerations and in accordance with previous literature findings as cited below. Furthermore, these four z-scored domains were equally integrated into a broad global cognitive index (GCI).

Attention: To assess attentional capacity, we focused primarily on sustained attention by including the two RVP parameters discrimination performance A' and total of hits.[1] In order to diversify this domain we added the RAVLT test parameter trial 1, a supraspan measure with a large attentional component.[2]

Working Memory: The SWM parameter number of total errors tested the capability to retain spatial information and to manipulate remembered items in working memory.[3] The LNST measured the verbal working memory by summing up the number of correct responses.[4] The third parameter was the number of correctly located patterns after the first presentation, a PAL parameter measuring primarily a visual working memory component.[5]

Declarative memory: The RAVLT was administered to assess the verbal declarative memory performance.[6] Performance was measured by the parameters learning performance (∑trials 1-5), delayed recall (trial 7), and an adjusted recognition performance (p(A)).[6] To capture the visual declarative memory, we used the two PAL parameters: adjusted total of errors and adjusted total of trials.[5]

Executive Functions: Executive functions are commonly separated into the three components shifting, updating, and inhibition.[7] Since inhibition in CU is currently investigated in another study from our laboratory[8], we focused on shifting (IED) and updating tasks (SWM strategy, RAVLT recall consistency). The IED assessed visual discrimination, attentional set formation, maintenance, shifting, and flexibility.[9] The considered test parameters were the total of errors and trials adjusted to the amount of completed stages. Hereby, we added the SWM strategy score assessing the applied heuristic strategies[3], and the RAVLT recall consistency, a parameter impaired in patients with prefrontal lesions[10-12] and related with measures of executive functions.[13]

Table DS1: Intercorrelation cocaine use parameters in cocaine users

	1)	2)	3)	4)	5)	6)	7)	8)	9)	10)	11)	12)	13)
1) Cumulative dose (grams) log	1	*.24	*.22	***.57	.02	***.62	-.09	***.34	***.37	*.21*	***.39	***.36	***.81
2) Times per week		1	***.70	-.09	.09	.17	.15	.18	.14	*.23	.16	.18	**.32
3) Grams per week log			1	-.13	.04	.13	.13	.04	-.04	.18	-.01	.03	.19
4) Years of use				1	-.03	.06	-.10	***.42	***.37	***.37	***.39	***.42	***.56
5) Age of onset					1	.07	-.17	.16	.20	.05	.17	.17	.09
6) Maximum dose (grams/day)						1	-.09	.14	*.23	-.08	*.22	.16	***.72
7) CCQ sum score (0-70)							1	.03	-.01	-.03	.01	.02	-.12
8) Hair analysis Cocaine pg/mg								1	***.91	***.70	***.86	***1.00	***.59
9) Hair analysis Benzoylecgonine pg/mg									1	***.55	***.95	***.94	***.61
10) Hair analysis Cocaethylene pg/mg										1	***.62	***.68	***.33
11) Hair analysis Norcocaine pg/mg											1	***.89	***.60
12) Hair analysis $Cocaine_{total}$ pg/mg												1	***.61
13) Severity of cocaine use Index[a]													1

Analyses only for cocaine users (n=98; Hair samples were voluntary and are deficient for 1 recreational cocaine user).
Pearson's product-moment correlation. Significant correlations (two-tailed) are marked: *p<.05; **p<.01; ***p<.001.
[a] Severity of cocaine use Index corresponds to the mean of the z-transformed parameters cumulative dose, grams per week, years of use, maximum dose, and hair analysis $Cocaine_{total}$.

Table DS2: Correlations between cognitive test scores and cocaine use parameters in cocaine users

	Attention			Working memory			Declarative memory					Executive functions			
	RVP A'	RVP Hits	RAVLT Trial 1	LNST Score	SWM Error[d]	PAL First trial[d]	RAVLT ∑ Trials 1-5	RAVLT p(A)	RAVLT Trial 7	PAL Errors adj.[d]	PAL Trials adj.[d]	IED Errors adj.	IED Trials adj.	SWM Strat.[d]	RAVLT Recall cons.
Cumulative dose (grams) log[a]	*-.23	*-.22	***-.38	**-.30	***.33	*-.26	***-.43	**-.31	***-.34	**.29	**.29			*.24	***-.39
Cumulative dose (grams) log, adj.	**-.27	**-.26	***-.35	**-.27	**.27	*-.22	***-.39	**-.31	***-.35	*.25	*.22				***-.37
Times per week[a]							*-.20		-.17						*-.25
Grams per week log[a]															
Years of use[a]			*-.25	*-.21	**.32	*-.22	***-.33	*-.23	-.20	.17	.20			***.35	**-.31
Years of use, adj. age[b]			-.19		*.23		*-.25	*-.25	*-.20					*.24	**-.30
Maximum dose (grams/day)[a]	*-.21	*-.21		*-.20			*-.24	*-.23	*-.22	.18					-.18
CCQ sum score (0-70)[a]															
Hair analysis Cocaine pg/mg[a,c]			-.18		.19		*-.24		-.19					.19	
Hair analysis Benzoylecgonine			*-.24	*-.23	*.23		**-.31		*-.24	.19	*.22			*.22	
Hair analysis Cocaethylene pg/mg[a,c]					**.27									**.27	
Hair analysis Norcocaine pg/mg[a,c]			**-.27	*-.22	**.29		**-.31		*-.23	.17	*.20			*.21	
Hair analysis $Cocaine_{total}$ pg/mg[a,,c,e]			-.19		*.21		*-.26		*-.20					.20	
Severity of cocaine use Index[a,f]			**-.31	**-.26	*.26		**-.44	*-.25	**-.32	.20	*.21			*.25	**-.38

Analyses only for cocaine users (n=98). Correlations with a p-level below 10% are shown, while significant correlations are marked as follows: *p<.05; **p<.01; ***p<.001.
[a] Pearson's product-moment correlation. [b] Partial Correlation corrected for age.
[c] Hair samples were voluntary and are deficient for 1 recreational cocaine user.
[d] Two cocaine users were missing either SWM or PAL parameters due to technical problems.
[e] $Cocaine_{total}$ = Cocaine + Benzoylecgonine + Norcocaine.
[f] Severity of cocaine use Index corresponds to the mean of the z-transformed parameters cumulative dose, grams per week, years of use, maximum dose, and hair analysis $Cocaine_{total}$.

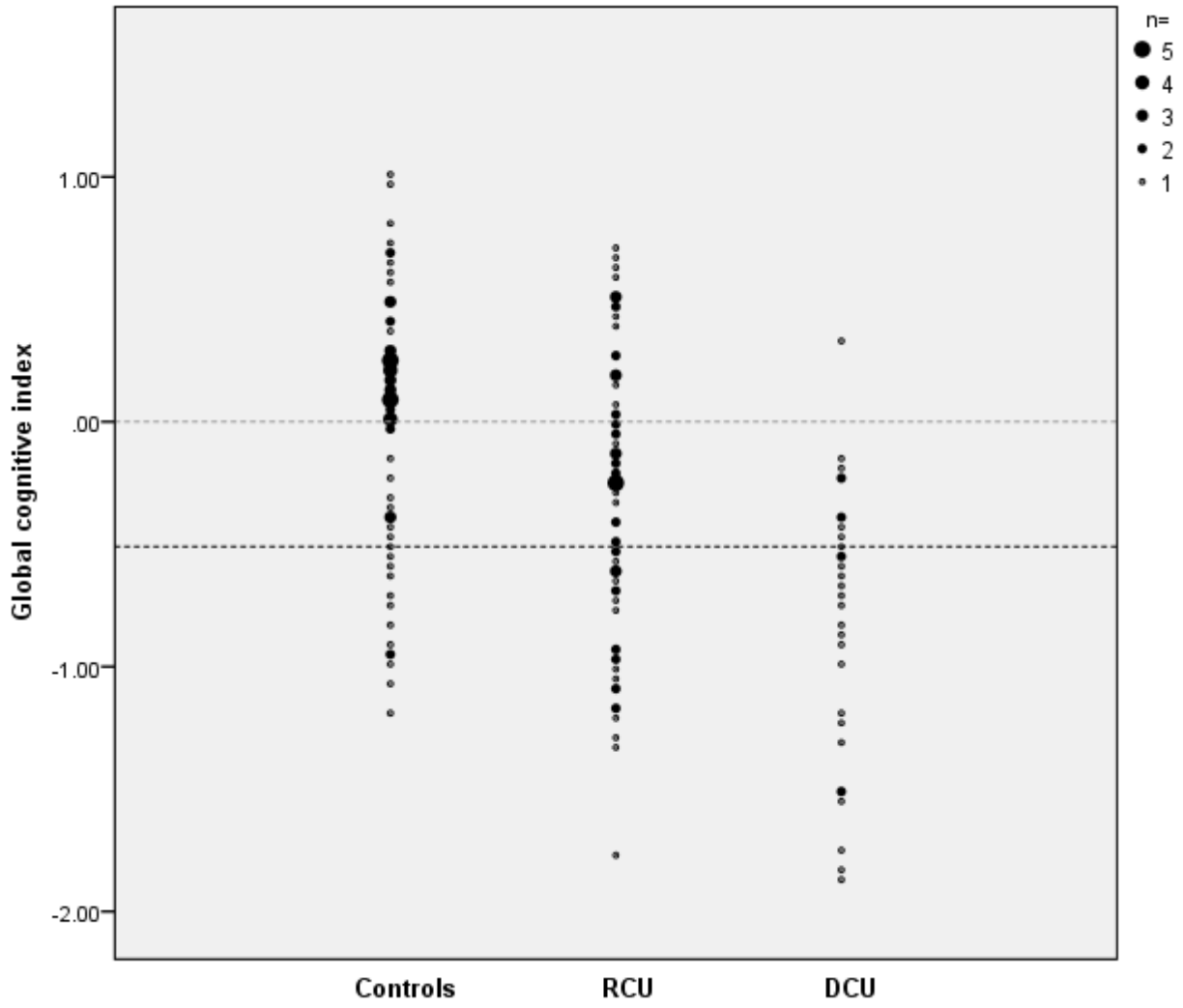
Table DS3: Predictors of the global cognitive index in cocaine users

	Model 1: Cumulative dose			Model 2: Years of use			Model 3: Weekly use		
	B	SE	β	B	SE	β	B	SE	β
Constant	.26	.33		-.10	.38		.53	.34	
Age	-.01	.01	-.16	.01	.02	.10	-.02	.01	**-.28
Depression	.00	.01	.04	.00	.01	.03	.00	.01	.02
ADHD	.00	.01	-.05	-.01	.01	-.11	-.01	.01	-.17
Craving for cocaine	-.01	.01	-.20	-.01	.01	-.15	-.01	.01	-.21
Urine sample (neg/pos)	.11	.14	.08	.08	.15	.05	.19	.14	.13
Cocaine cumulative dose (grams)	.00	.00	*-.29						
MDMA cumulative dose (tablets)	.00	.00	-.16						
Amphetamine cumulative dose (grams)	.00	.00	-.05						
Cannabis cumulative dose (grams)	.00	.00	-.08						
Cocaine years of use				-.04	.02	*-.29			
MDMA years of use				.00	.01	-.03			
Amphetamine years of use				.03	.02	.16			
Cannabis years of use				.00	.01	.05			
Alcohol years of use				.00	.02	-.01			
Nicotine years of use				-.02	.01	-.21			
Cocaine grams per week							.00	.01	-.02
MDMA tablets per week							-.15	.06	**-.25
Amphetamines grams per week							.11	.31	.03
Cannabis grams per week							-.01	.02	-.02
Alcohol grams per week							.00	.00	**.28
Cigarettes per week							.00	.00	*-.22
R^2			.22			.19			.29
F			**2.80			1.83			**3.20
p			.006			.06			.001

Multiple regression, only cocaine users (n= 98), *p<.05; **p<.01. Models included clinical variables linked to cognitive functioning (depression, ADHD, cocaine craving, and cocaine urine status) but included either cumulative, current, or duration of drug use parameters.
B, Unstandardized regression coefficient; SE, Unstandardized standard error; β, Standardized Beta.

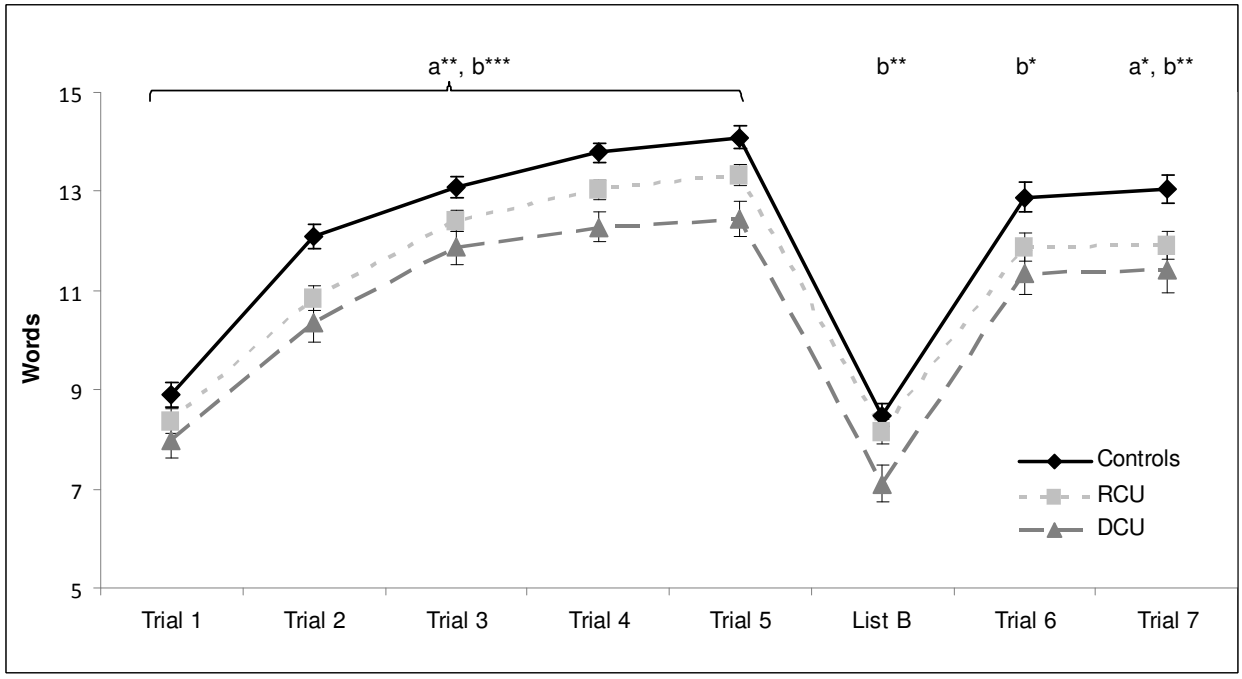
In the first model, cumulative cocaine dose was the only significant predictor for the GCI. In the second model, duration of cocaine use was again the only significant predictor for the GCI. The direction of the standardized beta coefficients reflected that increasing amount and duration of cocaine use was associated with decreased cognitive performance. In the third model, weekly consumption during the last 6 months could not account for a significant cocaine impact but was foremost influenced by age, the use of alcohol, cigarettes, and MDMA.

Figure DS1: GCI score scatterplot



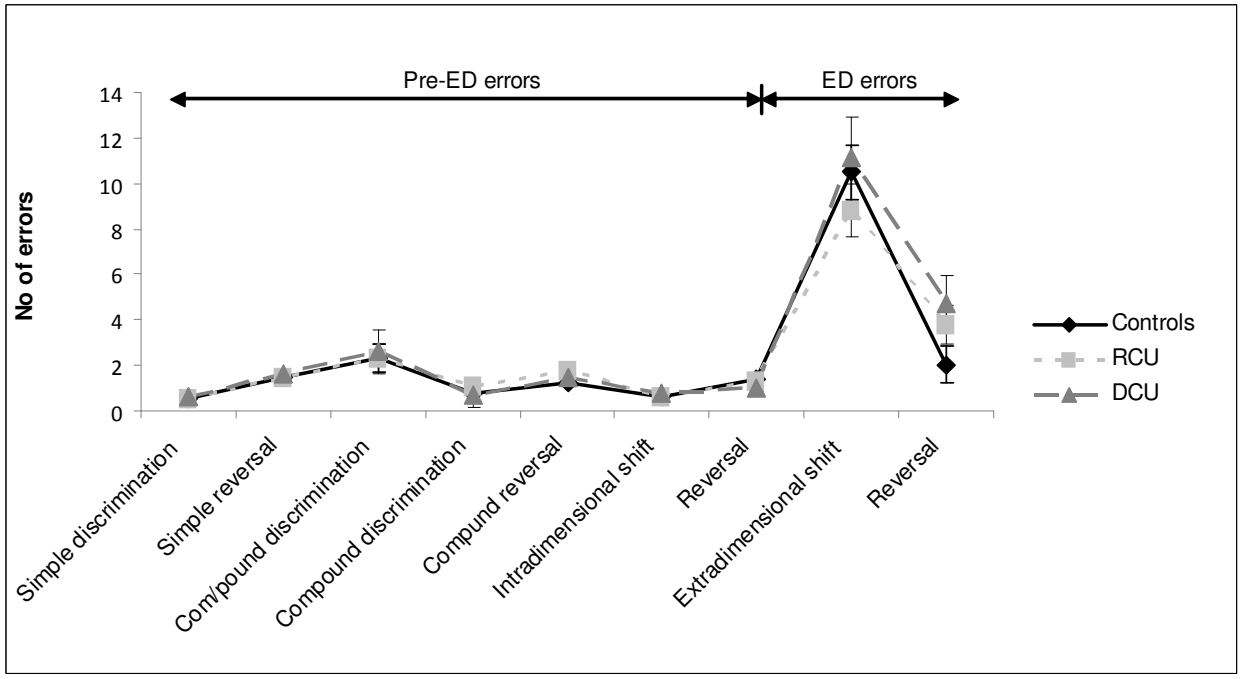
Separated for control group (n=68), recreational cocaine user group (n=68), and dependent cocaine user group (n=30). The dotted black line represents the clinical criterion of -1 SD of the control group.

Figure DS2: RAVLT performance



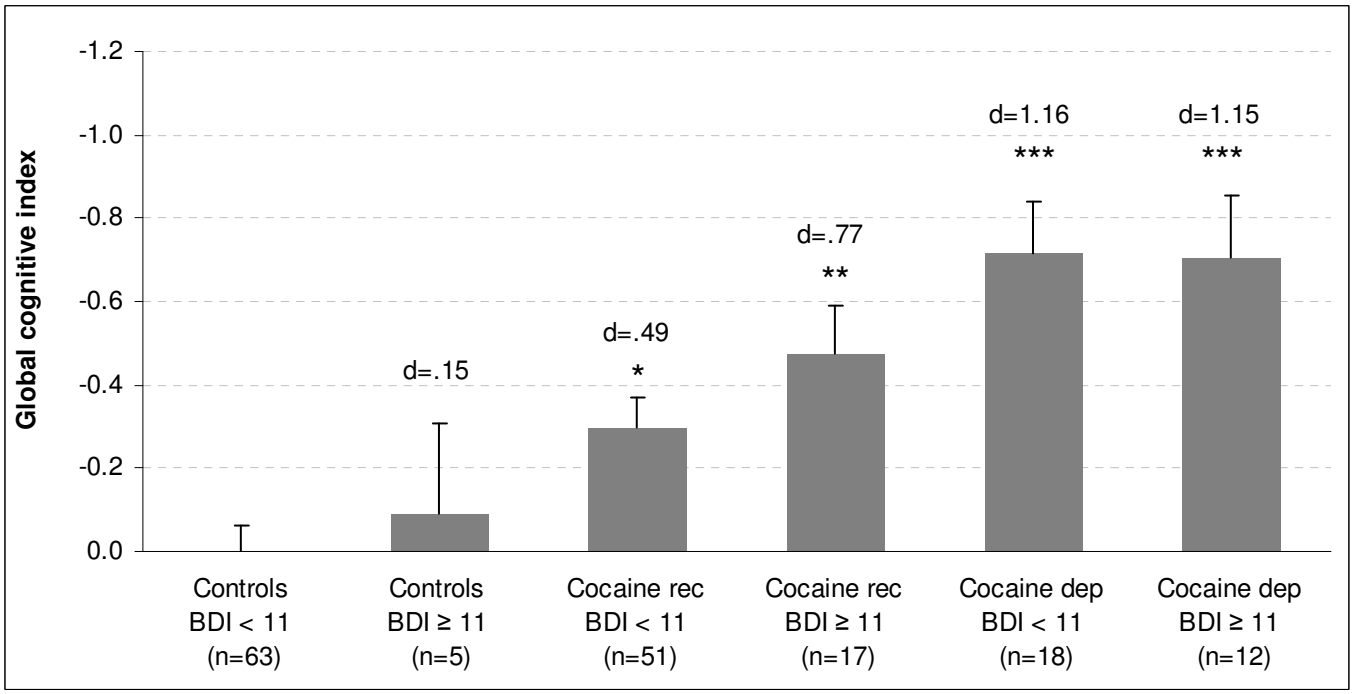
Performance in the first five learning trials, the interference list B, the recall after interference trial 6, and the delayed recall trial 7 in the Ray Auditory Verbal Learning Test (RAVLT). Means and standard errors (corrected for age and verbal IQ). Separated for control group (n=68), recreational cocaine user group (n=68), and dependent cocaine user group (n=30). [a] Sidak post hoc tests: Controls vs. Cocaine rec. [b] Sidak post hoc tests: Controls vs. Cocaine dep. *p<.05, **p<.01, ***p<.001.

Figure DS3: IED performance



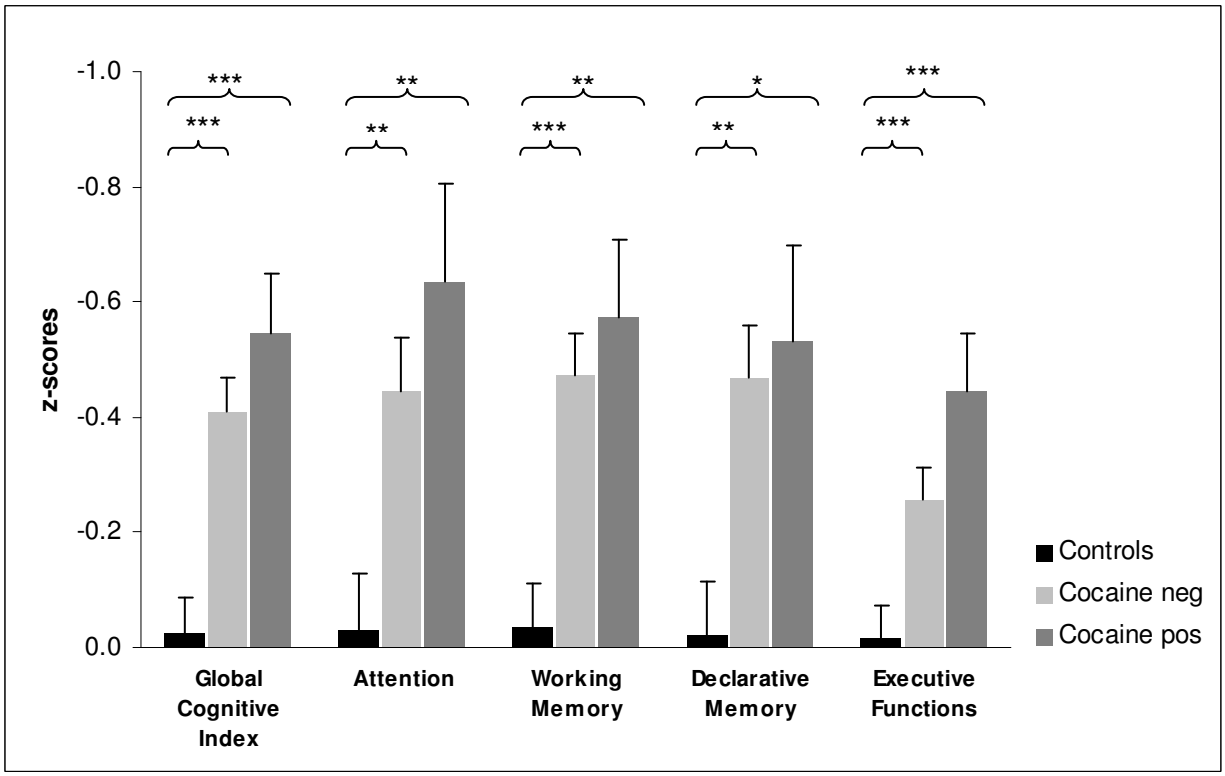
Error rates across the nine stages of the Intra/Extradimensional Attentional Set Shifting task (IED). Means and standard errors (corrected for age and verbal IQ). Separated for control group (n=68), recreational cocaine user group (n=68), and dependent cocaine user group (n=30). No significant pairwise Sidak post hoc tests.

Figure DS4: Impact depression status



Mean GCI scores and standard errors in groups stratified for cocaine use and BDI score. Values are corrected for age, verbal IQ, and cocaine gram/week. Group sizes (n) are shown. Significant Sidak post-hoc test vs. reference control group low depression (on the very left): *p<.05; **p<.01; ***p<.001. Cohen's d vs. control group low depression (on the very left).

Figure DS5: Impact current cocaine effects tested by urine status



Mean z-scores and standard errors for the global cognitive index and the four cognitive domains (values corrected for age and verbal IQ) in groups with controls (n=68), negative (n=75), and positive (n=22) urine samples. One hair sample (recreational cocaine user) was deficient. Sidak post-hoc tests: *p<.05; **p<.01; ***p<.001.

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